Remarks

Applicants thank Examiner DiBrino for the helpful interview held January 31, 2008. This paper includes the substance of the interview.

Amendments to the Claims

The amendments to the claims do not add new matter. The amendments to independent claim 1 (and the corresponding amendments to claims 12, 14, 15, and 48 and to withdrawn claims 16 and 76-80) are fully supported in provisional application Serial No. 60/395,781 filed July 12, 2002 as well as in the present specification, which incorporates Serial No. 60/395,781 by reference (par. [01]). Beads which comprise anti-CD28 antibodies and the recited MHC class I-immunoglobulin complex are disclosed, *e.g.*, on pages 6-7 of Serial No. 60/395,781 and in Example 1 of the present application (see par. [160]; "HLA-Ig" is the MHC class I-immunoglobulin complex, as described in U.S. Patent 6,268,411).

Obviousness Rejections

The Final Office Action contains nine obviousness rejections based on various combinations of six references. Because this amendment cancels claims 3, 7, 10, 23-29, 37, 39-41, 46, 47, 60-62, 64, 65, and 143-145 and because claims 16 and 71-87 are withdrawn, only the rejections of claims 1, 12-16, 48, and 49 are discussed below.

Section 103(a) of 35 U.S.C. states:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was

> made to a person having ordinary skill in the art to which said subject matter pertains.

Obviousness under 35 U.S.C. § 103(a) is a question of law based on several factual inquiries:

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved.

Graham v. John Deere Co., 383 U.S. 1, 17 (1966). The U.S. Patent and Trademark Office bears the initial burden of establishing a *prima facie* case of obviousness based on the results of the factual inquiries under *Graham*. A *prima facie* case of obviousness has three elements:

> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

Manual of Patent Examining Procedure, 8th ed., § 2142. In the present application, the results of the factual inquiries under *Graham v. John Deere Co.* do not support a *prima facie* case that any of claims 1, 12-15, 48, and 49 are obvious under 35 U.S.C. § 103(a) over any of the cited combinations of references.

I. Rejection under 35 U.S.C. § 103(a) over U.S. Patent 6,268,411 in view of WO 97/28191 and Latouche[1] (page 3, item 5)

Applicants respectfully traverse the rejection of claims 1, 12-15, 48, and 49 over U.S. Patent 6,268,411 in view of WO 97/28191 and Latouche.

[1] Latouche & Sadelain, "Induction of human cytotoxic T lymphocytes by artificial antigen-presenting cells," *Nature Biotechnology 18*, 405-09, April 2000.

1. Scope and content of the prior art

The first factual inquiry under *Graham* is to determine the scope and content of the prior art. 383 U.S. at 17. The scope and content of the cited prior art is described below.

a. U.S. Patent 6,268,411

The '411 patent discloses the MHC class I-immunoglobulin complex recited in claims 1, 12-15, 48, and 49. The '411 patent teaches that the complex can be "affixed to a solid substrate, such as a glass or plastic slide or tissue culture plate or latex, polyvinylchloride, or polystyrene beads." Col. 9, lines 63-67. The '411 patent also teaches that the complex can be "conjugated to molecules which stimulate an immune response, such as lymphokines or other effector molecules." Col. 10, lines 16-18. The '411 patent does not teach or suggest a bead and which comprises the MHC class I-immunoglobulin complex and an antibody that specifically binds to CD28.

b. WO 97/28191

WO 97/28191 teaches molecular complexes which the Office Action acknowledges differ from those recited in the pending claims.[2] The molecular complexes can be anchored to cell membranes of naturally occurring "host compatible antigen presenting cells." Page 33, lines 13-16. WO 97/28191 does not teach or suggest anchoring the disclosed molecular complexes to a bead or any other type of rigid substrate.

c. Latouche

Latouche discloses artificial antigen presenting cells (aAPC) made by transfecting NIH 373 cells with tumor antigen and relevant HLA A2 complexes and the use of the cells to stimulate selectively growth of antigen-specific CD8 T cells. Latouche teaches that there are a

[2] For example, the molecular complexes are single chain complexes (page 3, lines 7-25) and do not contain a immunoglobulin heavy chain variable region (*e.g.*, Figure 1C).

variety of co-stimulatory complexes, including the interaction of CD28 with B7-1 or B7-2, and that there is an important role of the addition of cytokine. Latouche teaches that the selective stimulation of antigen-specific CD8 T cells is based on HLA antigen density. Latouche speculates that beads coated with anti-CD3 and anti-CD28 antibodies might expand antigen-specific $CD4^+$ and $CD8^+$ T cells.

2. Differences between the prior art and the pending claims

The second factual inquiry under *Graham* is to ascertain the differences between the prior art and the claims at issue. 383 U.S. at 17. Each of the rejected claims recites a bead (*i.e.*, which is rigid) which comprises an MHC class I-immunoglobulin complex and an antibody that specifically binds to CD28. Nothing in any of the cited prior art teaches or suggests this combination. The combination of a co-stimulatory molecule and a molecular complex which can present an antigen is taught in association with naturally occurring cells in Latouche (fibroblasts) and WO 97/28191 (antigen presenting cells). The combination of a rigid solid support and a molecular complex which can present an antigen, taught in the '411 patent, does not include an antibody that specifically binds to CD28.

3. Level of skill in the art

The third factual inquiry under *Graham v. John Deere Co.* is to resolve the level of skill in the pertinent art. 383 U.S. at 17. The person of ordinary skill is described in *Custom Accessories, Inc. v. Jeffrey-Allan Industries, Inc.*:

> The person of ordinary skill is a hypothetical person who is presumed to be aware of all the pertinent prior art. The actual inventor's skill is not determinative. Factors that may be considered in determining level of skill include: type of problems encountered in art; prior art solutions to those problems; rapidity with which innovations are made; sophistication of the technology; and educational level of active workers in the field. Not all such

> factors may be present in every case, and one or more of them may predominate.

807 F.2d 955,962-63, 1 U.S.P.Q.2d 1196, 1201 (Fed. Cir. 1986).

At the July 12, 2002 priority date of this application, the person of ordinary skill would also have understood that the "the definitive event governing a mature immune response when T lymphocyte or natural killer (NK) cells interact with target cells is the formation of an immunological synapse."[3] The immunological synapse is a "clearly organized pattern of protein complexes, several microns in diameter, that forms at the junction between the membranes of the two cells" and requires that the proteins be able to move and reorganize in the cell membranes.[4]

The person of ordinary skill, being aware of all pertinent prior art relating to artificial antigen presenting cells, would have been aware that membrane fluidity was important. For example, Albani[5] teaches artificial antigen presenting cells (AAPCs), which are liposomes to which are anchored "an MHC:antigen complex" and, optionally, a co-stimulatory molecule. ¶¶ [0045]-[0046]. Albani teaches that the "free floating format" of the liposome is important for proper functioning of the AAPCs:

> [0050] The current invention's use of co-stimulatory, adhesion and other accessory molecules in a "free floating" format also helps to both anchor and direct the interaction between MHC:antigen:accessory molecule and T cell receptors by providing a means by which T cells in the sample will be presented with a structure more similar to that found in the natural state. Specifically, the MHC:antigen:accessory molecule complexes in conjunction with other functional molecules are able to migrate in proper orientation in the lipid bilayer of the liposome because of

[3] Qi *et al.*, *Proc. Natl. Acad. Sci. USA 98*, 6548-53, published on-line May 22, 2001, at page 6548, col. 1 ¶ 1 (internal references omitted); provided in the IDS that accompanies this paper.

[4] *Id.*

[5] Albani, "Methods for isolation, quantification, characterization and modulation of antigen-specific T cells," U.S. Patent 6,787,154, provided in the IDS filed April 27, 2007.

> the use of a unique combination of lipids and surfactant molecules, namely an optimal ratio of phosphatidylcholine and cholesterol respectively, included in the liposome matrix. These provide particular protein presentation characteristics and easy protein migration properties to the surface of the liposome structure so that the MHC:antigen complexes can easily migrate to T cell binding loci similar to "capping" events seen in natural APCs. Moreover, as shown in the figures, the structure of our artificial APC liposomes allows for specific "capping" of the liposomes on the surface of the T cells to which the liposomes are bound.

Albani teaches that a liposome-based AAPC can be anchored to a solid support, but that only the lipid component itself – not any of the functional molecules it contains – is bound to the solid support. ¶ [0084].

Additional evidence for the importance of a fluid membrane is discussed in the accompanying Declaration of Drs. Schneck and Oelke under 37 C.F.R. § 1.132 and summarized in paragraph 9 of the Declaration. For details, see paragraphs 6 (Deeths[6]), 7 (Laux[7]), and 8 (Maus[8]) of the Declaration.

4. Failure to establish a *prima facie* case of obviousness

The U.S. Patent and Trademark Office bears the burden of establishing a *prima facie* case of obviousness under 35 U.S.C. § 103; only when a *prima facie* case has been established does the burden shift to the applicants to provide evidence or argument in rebuttal. *In re Rijckaert*, 9 F.3d 1531, 1532, 28 U.S.P.Q.2d 1955, 1966 (Fed. Cir. 1993), *citing In re Oetiker*, 977 F.2d

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[6] Deeths & Mescher, "B7-1-dependent co-stimulation results in qualitatively and quantitatively different responses by $CD4^+$ and $CD8^+$ T cells," *Eur. J. Immunol. 27*, 598-608, 1997, provided with the IDS filed April 27, 2007.

[7] Laux *et al.*, "Response differences between human $CD4^+$ and $CD8^+$ T-cells during CD28 costimulation: implications for immune cell-based therapies and studies related to the expansion of double-positive T-cells during aging," *Clin. Immunol. 96*, 189-97, 2000, provided with the IDS which accompanies this paper.

[8] Maus *et al.*, "*Ex vivo* expansion of polyclonal and antigen-specific cytotoxic T lymphocytes by artificial APCs expressing ligands for the T-cell receptor, CD28 and 4-1BB," *Nature Biotechnology 20*, 143-48, 2002, provided with the IDS filed April 27, 2007.

1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992). In this case, the results of the factual inquiries carried out under *Graham* do not support a *prima facie* case that any of the rejected claims is obvious.

A *prima facie* case of obviousness requires that the cited references themselves or the knowledge generally available to one of ordinary skill in the art contain a suggestion or motivation to combine the reference teachings and that there must be a reasonable expectation of success that the combination would be successful. M.P.E.P. § 2142. Neither requirement is met.

The obviousness rejection is based on the speculation in Latouche that anti-CD3mAb and anti-CD28mAb bound to beads (CD3/CD28-beads) might be used for large scale T cell expansion of both $CD4^+$ and $CD8^+$ antigen-specific T cells; therefore, it would allegedly have been obvious to use the artificial antigen presenting cell recited in the pending claims to expand antigen-specific $CD4^+$ and $CD8^+$ cells. As explained above, however, one of ordinary skill in the art would have known that formation of an immunological synapse between a T cell and an antigen presenting cell requires membrane fluidity. Albani, WO 97/28191, Latouche, and Maus all teach artificial antigen presenting cells which have fluid membranes. One of ordinary skill would have been aware of these teachings and – despite the speculation in Latouche – would not have been motivated to use a bead, which is rigid, as an artificial antigen presenting "cell" comprising an antibody that specifically binds to CD28 and the MHC class I-immunoglobulin complex taught in the '411 patent because the ordinary artisan would not have had a reasonable expectation that the molecules would have been able to reorganize into the required immunological synapse. Moreover, the ordinary artisan would have known of the unsuccessful attempts of Deeths, Laux, and Maus to expand $CD8^+$ T cells using bead-based artificial APCs.

For this reason, as the accompanying Declaration of Drs. Jonathan Schneck and Mathias Oelke under 37 C.F.R. § 1.132 explains, it was surprising unexpected that beads with the features recited in claim 1 did support large scale antigen-specific $CD8^+$ expansion. See Example 4 in the present specification and paragraphs 11-13 of the Declaration. Thus, even if, *arguendo*, a *prima facie* case of obviousness over the combination of over U.S. Patent 6,268,411, WO 99/42597, and WO 97/28191 could be made, Applicants can rebut the *prima facie* case with the unexpected results described in paragraphs 11-13 of the accompanying Declaration and in the present specification.

Please withdraw the rejection.

II. Rejection under 35 U.S.C. § 103(a) over U.S. Patent 6,268,411 in view of WO 99/42597 and WO 97/28191 (page 13, item 8)

Applicants respectfully traverse the rejection of claims 1, 12-15, 48, and 49 under 35 U.S.C. § 103(a) over U.S. Patent 6,268,411 in view of WO 99/42597 and WO 97/28191 and a statement in paragraph [83] of the present application.

The scope and content of the '411 patent and WO 97/28191, the differences between those references and the pending claims, and the level of skill in the art are discussed above. WO 99/42597 teaches fusion proteins which contain a binding domain of an MHC chain towards the N-terminus and a dimerization domain (such as a leucine zipper domain or an immunoglobulin Fab constant domain) toward the C-terminus. *E.g.*, page 4, lines 10-12; page 4, line 28 to page 5, line 5; page 9, lines 11-19. Multiple fusion proteins can be attached to a carrier such as a spherical or porous bead to form a conjugate. Page 8, lines 3-27. Either the fusion

proteins or the conjugates can be "associated with, or bound to" various accessory molecules, *e.g.*, for killing, modulating, anergizing, or activating T cells (page 45, lines 21-28).

Claims 1, 12-15, 48, and 49 are not obvious over the cited combination of U.S. Patent 6,268,411, WO 99/42597, and WO 97/28191. First, as explained above, one of ordinary skill would not have been motivated to make the rigid artificial antigen presenting "cell" to which the pending claims are directed because the ordinary artisan would not have had a reasonable expectation that the recited molecules would have been able to reorganize into the required immunological synapse. WO 99/42597 does not contain any working examples of bead-based conjugates which would cause the ordinary artisan to change this expectation.

Second, even if, *arguendo*, a *prima facie* case of obviousness over the combination of over U.S. Patent 6,268,411, WO 99/42597, and WO 97/28191 could be made, Applicants can rebut the *prima facie* case with the unexpected results described in paragraphs 11-13 of the accompanying Declaration.

Please withdraw the rejection.

III. Obviousness-type double patenting rejection over claims 1-104 of U.S. Patent 6,268,411 in view of WO 97/35991, WO 97/28191, and Latouche (page 20, item 11)

Applicants respectfully traverse the obviousness-type double patenting rejection of claims 1, 12-15, 48, and 49 over claims 1-104 of U.S. Patent 6,268,411 in view of WO 97/35991, WO 97/28191, and Latouche.

An obviousness-type double patenting analysis parallels an analysis under 35 U.S.C. § 103(a) except that the disclosure of the cited patent is not considered prior art. *In re Braat,* 937

F.2d 589, 592, 19 U.S.P.Q.2d 1289, 1291-92 (Fed. Cir. 1991); *In re Braithwaite*, 379 F.2d 594, 600, footnote 4, 154 U.S.P.Q. 29, 34, footnote 4 (C.C.P.A. 1967). Thus, the arguments made in sections I and II, above, apply with equal force to the obviousness-type double patenting rejection and are incorporated herein. Contrary to the Office Action's statement in the last paragraph on page 20, WO 97/35991 teaches only MHC class II complexes. These complexes are no longer recited in the pending claims.

Please withdraw the rejection.

IV. Rejection under 35 U.S.C. § 103(c) over claims 1-104 of U.S. Patent 6,268,411 in view of WO 97/35991, WO 97/28191, and Latouche (page 22, item 12)

Applicants respectfully traverse the rejection of claims 1, 12-15, 48, and 49 under 35 U.S.C. § 103(c) over claims 1-104 of U.S. Patent 6,268,411 in view of WO 97/35991, WO 97/28191, and Latouche. The arguments made above in sections I, II, and III apply with equal force to the rejection under 35 U.S.C. § 103(c) and are incorporated herein.

Please withdraw the rejection.

V. Remaining obviousness rejections

The Final Office Action contains four obviousness rejections which cite as the primary reference Schneck & O'Herrin, U.S. Patent 6,015,884.[9] A fifth rejection cites as the primary reference WO 97/35991;[10] WO 97/35991 has the same specification as the '884 patent. Both the

[9] These are rejections under 35 U.S.C. § 103(a) set forth in the Final Office Action on page 7, item 6 and page 17, item 9; an obviousness-type double patenting rejection on page 23, item 14; and a rejection under 35 U.S.C. § 103(c) on page 25, item 15.

[10] This is a rejection under 35 U.S.C. § 103(a) set forth in the Final Office Action on page 11, item 7.

'884 patent and WO 97/35991 disclose only MHC class II molecular complexes, and this subject matter has been deleted from the pending claims to advance prosecution.

None of the secondary references cited in these five obviousness rejections (WO 97/35991, Latouche, WO 97/28191, and WO 99/42597) teaches or suggests the MHC class I-immunoglobulin complexes recited in the pending claims. Thus, none of the remaining combinations of references teaches or suggests all the elements recited in the claims. For at least this reason, there is no *prima facie* case of obviousness based on these combinations of references.

Respectfully submitted,

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